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(54) CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITIONS

GESCHMACKSMASKIERTE ORALE PHARMAZEUTISCHE ZUSAMMENSETZUNGEN MIT KONTROLLIERTER ABGABE

COMPOSITIONS PHARMACEUTIQUES ADMINISTRABLES PAR VOIE ORALE A LIBERATION CONTROLEE ET GOUT MASQUE

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Description

[0001] The present invention relates to controlled release and taste-masking compositions containing one or more active principles incorporated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally incorporated or dispersed in hydrophilic matrices. The use of a plurality of systems for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract, and it also allows the oral administration of active principles having unfavourable taste characteristics or irritating action on the mucosae of the administration site, particularly in the buccal area.

[0002] The compositions of the invention can contain active principles belonging to the therapeutical classes of analgesics, antiinflammatories, cardioactives, tranquilizers, antihypertensives, disinfectants and topical antimicrobials, antiparkinson drugs, antihistamines and are suitable to the oral administration or for acting topically at some areas of the gastrointestinal tract.

TECHNOLOGICAL BACKGROUND

[0003] The preparation of a sustained, controlled, delayed or anyhow modified release form can be carried out according to different known techniques:

1. The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.
2. The use of hydrophilic matrices, in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.
3. The use of bioerodible matrices, which are capable of being degraded by the enzymes of some biological compartment.

[0004] All the procedures listed above suffer, however, from drawbacks and imperfections.

[0005] Inert matrices, for example, generally entail nonlinear, but exponential, release of the active ingredient.

[0006] Hydrophilic matrices have a linear behaviour until a certain fraction of active ingredient has been released, then they significantly deviate from linear release.

[0007] Bioerodible matrices are ideal to carry out the so-called "site-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, the frequently release in situ metabolites that are not wholly toxicologically inert.

[0008] A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001-1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated.

[0009] The same notion of canalization of an inert matrix is described in US 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetration of different matrix materials.

[0010] EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for the their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form.

[0011] The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3), 531-533, , (1998) which improves the application through an annealing technique of the inert polymer layer which is deposited on the surface of the pellets.

[0012] DE 4131562 discloses pharmaceutical compositions comprising a solid core consisting of lipophilic compounds in which the active agent is inglobated, a stabilising agent such as lecithin; and an aqueous medium in which the lipophilic phase is dispersed.

[0013] To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in hydrophilic matrix which comprises:

- dissolution of the active ingredient with gastro-resistant hydrophilic polymers in organic solvents;
- drying of said suspension;
- subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application.

[0014] EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid.

[0015] WO 95/18451 discloses a composition only formed by a hydrophilic matrix coated with a gastro-re-

sistant film for controlling the dissolution rate of the active ingredient.

[0016] When preparing sustained-, controlled- release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release.

[0017] Said object has been attained according to the present invention, through the combination of an amphiphilic matrix inside an inert matrix, the latter formulated with a lipophilic polymer in a superficial hydrophilic matrix. The compositions of the invention are characterized by the absence of a first phase in which the medicament superficially present on the matrix is quickly solubilized, and by the fact the the amphiphilic layer compensate the lack of affinity of the aqueous solvent with the lipophilic compounds forming the inner inert matrix.

DISCLOSURE OF THE INVENTION

[0018] The invention provides controlled release and taste masking oral pharmaceutical compositions containing an active ingredient, comprising:

a) a matrix consisting of lipophilic compounds with melting point lower than 90°C and optionally by amphiphilic compounds in which the active ingredient is at least partially incorporated;
b) an amphiphilic matrix;
c) an outer hydrophilic matrix in which the lipophilic matrix and the amphiphilic matrix are dispersed;
d) optionally other excipients.

[0019] A further aspect of the invention provides taste masking oral pharmaceutical compositions containing one or more active ingredients comprising:

- an inert or lipophilic matrix consisting of C6-C20 alcohols or C8-C20 fatty acids or esters of fatty acids with glycerol or sorbitol or other polyalcohols with carbon atom chain not higher than six;
- an amphiphilic matrix consisting of polar lipids of type I or II or glycols partially etherified with C1-C4 alkyl chains;
- an outer hydrophilic matrix containing the above matrices, mainly formed by saccharide, dextrin, polyalcohol or cellulose compounds or by hydrogels;
- optional excipients to give stability to the pharmaceutical formulation.

DETAILED DISCLOSURE OF THE INVENTION

[0020] The compositions of the invention can be prepared by a method comprising the following steps:

a) the active ingredient is first inglobated by simple kneading or mixing in a matrix or coating consisting of compounds having amphiphilic properties, which will be further specified below. The active principle (s) can be mixed with the amphiphilic compounds without the aid of solvents or with small amounts of water-alcoholic solvents.

b) The matrix obtained in a) is incorporated in a low melting lipophilic excipient or mixture of excipients, while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion. After cooling at room temperature an inert matrix forms, which can be reduced in size to obtain inert matrix granules containing the active ingredient particles.

c) The inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellable excipients. The mixture is then subjected to compression or tabletting. This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix.

[0021] The amphiphilic compounds which can be used according to the invention comprise polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolamine), ceramides, glycol alkyl ethers such as diethylene glycol monomethyl ether (Transcutol(R)).

[0022] The lipophilic matrix consists of substances selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerids, the polyethoxylated derivatives thereof, waxes, ceramides, cholesterol derivatives or mixtures thereof having melting point within the range of 40 to 90°C, preferably from 60 to 70°C.

[0023] If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside.

[0024] An amphiphilic matrix with high content in active tegredient, typically from 5 to 95% w/w, is first prepared by dispersing the active ingredient or the mixture of active ingredients in a mixture of amphiphilic compounds, such as lecithin, other type II polar lipids, surfactants , or in diethylene glycol monoethyl ether; the resulting amphiphilic matrix is then mixed or kneaded, usually while hot, with lipophilic compounds suitable to form an inert matrix, such as saturated or unsaturated fatty acids, such as palmitic, stearic, myristic, lauric, lauryllic, or oleic acids or mixtures thereof with other fatty

acids with shorter chain, or salts or alcohols or derivatives of the cited fatty acids, such as mono-, di-, or triglycerids or esters with polyethylene glycols, alone or in combination with waxes, ceramides, cholesterol derivatives or other apolar lipids in various ratios so that the melting or softening points of the lipophilic compounds mixtures is within the range of 40° to 90°C, preferably from 60 to 70°C.

[0025] Alternatively, the order of formation of the inert and amphiphilic matrices can be reversed, incorporating the inert matrix inside the amphiphilic compounds.

[0026] The resulting inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture.

[0027] The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which when passing from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves.

[0028] Examples of hydrogels which can be used according to the invention are compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid.

[0029] In case of taste-masking formulations, the use of polyalcohols such as xylitol, mafitol and mannitol as hydrophilic compounds can also be advantageous.

[0030] The lipophilic matrix granules containing the active ingredient are mixed with the hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:50 (lipophilic matrix: hydrophilic matrix). Part of the active ingredient can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hycrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitablets.

[0031] The compression of the mixture of lipophilic and/or amphiphilic matrix, hydrogel-forming compound and, optionally, active ingredient not inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix. A similar result can also be obtained by coating the lipophilic matrix granules with a hydrophilic polymer coating.

[0032] The tablets obtainable according to the invention can optionally be subjected to known coating processes with a gastro-resistant film, consisting of, for example, methacrylic acids polymers (Eudragit®) or cellulose derivatives, such as cellulose acetophthalate.

[0033] Active ingredients which can conveniently be formulated according to the invention comprise:

- analgesics, such as acetaminophen, phenacetin, sodium salicylate;
- antitussives, such as dextromethorphan, codeine phosphate;
- bronchodilators, such as albuterol, procaterol;
- antipsychotics, such as haloperidol, chlorpromazine;
- antihypertensives and coronary-dilators, such as isosorbide mono- and dinitrate, captopril;
- selective β 2 antagonists, such as salbutamol, terbutaline, ephedrine, orciprenaline sulfate;
- calcium antagonists, such as nifedipine, nicardipine, diltiazem, verapamil;
- antiparkinson drugs, such as pergolide, carpidopa, levodopa;
- non steroid anti-inflammatory drugs, such as ketoprofen, ibuprofen, diclofenac, diflunisal, piroxicam, naproxen, ketorolac, nimesulide, tiaprophenic acid, mesalazine (5-aminosalicylic acid);
- antihistamines, such as terfenedine, loratadine;
- antidiarrheals and intestinal antiinflammatories, such as loperamide, 5-aminosalicylic, olsalazine, sulfasalazine, budesonide;
- spasmolytics such as octylonium bromide;
- anxiolytics, such as chlordiazepoxide, oxazepam, medazepam, alprazolam, donazepam, lorazepan;
- oral antidiabetics, such as glipizide, metformin, phenformin, gliclazide, glibenclamide;
- cathartics, such as bisacodil, sodium picosulfate;
- antiepileptics, such as valproate, carbamazepine, phenytoin, gabapentin;
- antitumorals, such as flutamide, etoposide;
- oral cavity disinfectants or antimicrobials, such as benzalkonium chloride, cetylpyridinium chloride or tibezonium iodide, and some amino derivatives such as benzydamine and chlorhexidine as well as the salts and derivatives thereof;
- sodium fluoride.

[0034] The compositions of the invention can further contain conventional excipients, for example bioadhesive excipients such as chitosans, polyacrylamides, natural or synthetic gums, acrylic acid polymers.

[0035] The compositions of the invention can contain more than one active ingredient, each of them being optionally contained in the hydrophilic matrix or in the inert amphiphilic matrix, and are preferably in the form of tablets, capsules or minitablets.

[0036] In terms of dissolution characteristics, contact with water or aqueous fluids causes the immediate penetration of water inside the more superficial layer of the matrix which, thanks to the presence of the aqueous solvent, swells due to the distension of the polymeric chains of the hydrogels, giving rise to a high viscosity hydrated front which prevents the further penetration of

the solvent itself linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness, until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of inert matrix granules, however induces the diffusion mechanism typical of these structures and therefore further slows down the dissolution profile of the active ingredient.

[0037] The presence of the amphiphilic matrix inside the lipophilic matrix inert allows to prevent any unevenness of the release profile of the active ingredient. The surfactants present in the amphiphilic portion promote wettability of the porous canaliculuses which cross the inert matrix preventing or reducing resistance to penetration of the solvent inside the inert matrix.

[0038] To obtain taste masking tablets, the components of the hydrophilic matrix are carefully selected to minimize the active substance release time through penetration accelerated by the canalization induced by the hydrophilic compound.

[0039] The following Examples illustrate the invention in greater detail.

EXAMPLE 1

[0040] 500 g of 5-aminosalicylic acid and 20 g of octylonium bromide are mixed with 10 g of soy lecithin dissolved in 50 g of a water - ethyl alcohol 1:3 mixture at about 50°C. After homogenization and drying, the granules of the resulting matrix are treated in a kneader with 20 g of carnauba wax and 50 g of stearic acid, heating until homogeneous dispersion, then cold-extruded into small granules. The inert matrix granules are loaded into a mixer in which 30 g of carbopol 971 P and 65 g of hydroxypropyl methylcellulose are sequentially added. After a first mixing step for homogeneously dispersing the powders, 60 g of microcrystalline cellulose and 5 g of magnesium stearate are added. After mixing, the final mixture is tabletted to unitary weight of 760 mg/tablet. The resulting tablets are film-coated with cellulose acetophthalate or polymethacrylates and a plasticizer to provide gastric resistance and prevent the early release of product in the stomach.

[0041] The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 30%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

EXAMPLE 2

[0042] 50 g of diethylene glycol monoethyl ether are homogeneously distributed on 500 g of microcrystalline cellulose; then 100 g of Budesonide are added, mixing to complete homogenization. This mix is further added with 400 g of Budesonide, then dispersed in a blender containing 100 g of carnauba wax and 100 g of stearic acid preheated at a temperature of 80°C. After kneading for 5 minutes, the mixture is cooled to room temperature and extruded in granules of size below 1 mm.

[0043] A suitable mixer is loaded with the matrix granules prepared as above and the following amounts of hydrophilic excipients: 1500 g of hydroxypropyl methylcellulose and 500 g of policarbophil.

[0044] The components are mixed until homogeneous dispersion of the matrices, then added with 2450 g of microcrystalline cellulose, 400 g of lactose, 100 g of colloidal silica and 50 g of magnesium stearate. After further 5 minute mixing, the mix is tabletted to unitary weight of 250 mg/tablet.

EXAMPLE 3

[0045] 850 g of metformin are dispersed in a granulator/kneader with 35 g of diethylene glycol monoethyl ether previously melted with 100 g of stearic acid and 55 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 1040 g of formulation are added with 110 g of hydroxypropyl methylcellulose and 20 g of magnesium stearate.

[0046] The final mixture is tabletted to unitary weight of 1170 mg/tablet equivalent to 850 mg of active ingredient.

[0047] The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 35%, after 180 minutes no more than 80%, after 5 hours no more than 80%.

EXAMPLE 4

[0048] 120 g of octylonium bromide are dispersed in a granulator/kneader with 30 g of stearic acid and 15 g of beeswax in which 10 g of diethylene glycol monoethylene had previously been melted.

[0049] The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 10 g of formulation are added with 5 g of hydroxypropyl methylcellulose and 5 g of policarbophyl, 2 g of magnesium stearate and 3 g of microcrystalline cellulose.

[0050] The final mixture is tabletted to unitary weight of 200 mg/tablet equivalent to 120 mg of active ingredient.

[0051] The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 25%, after 180 minutes no more than 60%, after 5 hours no more than 70%.

EXAMPLE 5

[0052] 12 g of diethylene glycol monoethyl ether are loaded on 6 g of microcrystalline cellulose and 6 grams

of calcium carbonate, then 100 g of Gabapentin are added and the mixture is homogenized. After that, 800 g of Gabapentin are added which are dispersed in a granulator/kneader with 4.5 g of white wax and 5 g of stearic acid. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 916.5 g of formulation are added with 39.5 g of hydroxypropyl methylcellulose, 10 g of alginic acid, 11 g of magnesium stearate and 6 g of syloid. The final mixture is tabletted to unitary weight of 1000 mg/tablet equivalent to 800 mg of active ingredient.

EXAMPLE 6

[0053] 50 g (25 g) of carbidopa and 200 g (100 g) of levodopa are dispersed in a granulator/kneader with 60 g (30 g) of stearic acid and 30 g (15 g) of yellow wax, in which 10 (5) g of diethylene glycol monoethyl ether had previously been melted.

[0054] The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 340 g (170 g) of formulation are added with 20 g (10 g) of hydroxypropyl methylcellulose, 10 g (5 g) of xantangum, 16 g (8 g) of microcrystalline cellulose, 4 g (2 g) of magnesium stearate.

[0055] The final mixture is tabletted to unitary weight of 400 (200) mg/tablet equivalent to 50(25) mg of carbidopa and 200 (100) mg di levodopa.

EXAMPLE 7

[0056] 4 g of Nimesulide are solubilised in 50 g of diethylene glycol monoethyl ether, then 100 g of microcrystalline cellulose are added to obtain a homogeneous mixture.

[0057] The resulting mixture is added in a granulator/kneader with 196 g of Nimesulide, 50 g of stearic acid and 25 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert and amphiphilic matrix system.

[0058] 425 g of the resulting granulate are added with 50 g of hydroxypropyl methylcellulose, 5 g of policarbophil and 10 g of magnesium stearate.

[0059] The final mixture is tabletted to unitary weight of 500 mg/tablet equivalent to 200 mg of active ingredient.

[0060] The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 1 hour no more than 25%, after 2 hours no more than 40%, after 4 hours no more than 60%, after 8 hours no more than 90%.

EXAMPLE 8

[0061] 500 g of propionyl carnitine are dispersed in a granulator/kneader with 90 g of stearic acid and 40 g of carnauba wax, in which 20 g of diethylene glycol monoethyl ether had previously been melted. The system is heated to carry out the granulation of the active ingredient in the inert/amphiphilic matrix. The resulting 650 g of formulation are added with 60 g of hydroxypropyl methylcellulose and 10 g of magnesium stearate.

[0062] The final mixture is tabletted to unitary weight of 720 mg/tablet equivalent to 500 mg of active ingredient.

[0063] The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 40%, after 180 minutes no more than 60%, after 4 hours no more than 80%, after 8 hours no more than 90%.

EXAMPLE 9

[0064] One kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with 200 g of cetyl alcohol and 25 g of glycerol palmitostearate; the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30°C. The resulting inert matrix is added, keeping stirring and kneading during cooling, with 50 g of soy lecithin and 50 g of ethylene glycol monoethyl ether. The granulate is extruded through a metallic screen of suitable size and mixed with 50 g of hydroxypropyl methylcellulose, 1520 kg of maltodextrins, 2 kg of lactose-cellulose mixture, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture is tabletted to unitary weight of about 500 mg, having hardness suitable for being dissolved in the mouth and a pleasant taste.

EXAMPLE 10

[0065] Operating as in the preceding example, chewable tablets are prepared replacing dextrin with mannitol and the lactose-cellulose mixture with xylitol. The resulting tablets ahve pleasant taste and give upon chewing a sensation of freshness enhancing the flavour.

EXAMPLE 11

[0066] Operating as described in example 8, but with the following components:

- active ingredient: ibuprofen mg 100
- lipophilic/inert matrix component: cetyl alcohol mg 15
- amphiphilic matrix component: soy lecithin mg 8
- hydrophilic matrix components: mannitol mg 167
- maltodextrins mg 150
- methylhydroxypropylcellulose mg 30
- adjuvants: aspartame mg 15
- flavour mg 5

- colloidal silica mg 5
- magnesium stearate mg 5

[0067] 500 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the bitter, irritating taste of the active ingredient.

EXAMPLE 12

[0068] Operating as described in example 9, but with the following components:

- active ingredient: diclofenac sodium mg 25
- lipophilic/inert matrix component: cetyl alcohol mg 5
- glycerol palmitostearate mg 5
- amphiphilic matrix component: soy lecithin mg 7
- hydrophilic matrix components: xylitol mg 168
- maltodextrins mg 150
- hydroxypropylmethylcellulose mg 20
- adjuvants: aspartame mg 5
- flavour mg 5
- colloidal silica mg 5
- magnesium stearate mg 5

[0069] 400 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

EXAMPLE 13

[0070] Operating as described in example 9, but with the following components:

- active ingredient: chlorhexidine mg 2,5
- lipophilic/inert matrix component: cetyl alcohol mg 0.5
- glycerol palmitostearate mg 0.5
- amphiphilic matrix component: diethylene glycol monoethyl ether mg 0,3
- hydrophilic matrix components: xylitol mg 38
- maltodextrins mg 96
- hydroxypropyl methylcellulose mg 10
- adjuvants: aspartame mg 3
- flavour mg 5
- colloidal silica mg 2
- magnesium stearate mg 2

[0071] 150 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

EXAMPLE 14

[0072] One Kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with g 125 of cetyl alcohol: the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30°C, then added with g 30 of lecithin. The resulting matrix is then extruded through a metallic screen of suitable size and mixed with 2.415 kg of lactose, 1.0 kg of maltodextrins, 50 g of hydroxypropyl methylcellulose, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture if tabletted to about 500 mg tablets, having hardness suitable for being dissolved in the mouth and pleasant taste.

Claims

1. Controlled release and taste-masking oral pharmaceutical compositions containing an active ingredient, comprising:

   a) a matrix consisting of lipophilic compounds with melting point lower than 90°C in which the active ingredient is at least partially ingiobated;
   b) an amphiphilic matrix;
   c) an other hydrophilic matrix consisting of hydrogels in which the lipophilic matrix and the amphiphilic matrix are dispersed;
   d) optionally other excipients.

2. Taste-masking formulations as claimed in claim 1 comprising a lipophilic matrix, an amphiphilic matrix and a hydrophilic matrix, in which the lipophilic matrix consists of C6-C20 alcohols or C8-C20 fatty acids or esters of fatty acids with glycerol or sorbitol or other polyalcohols with carbon atom chain not higher than six.

3. Compositions as claimed in any one of claims 1 to 2 in which the amphiphilic compounds are polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolamine), ceramides, glycol alkyl ethers, esters of fatty acids with polyethylene glycols or diethylene glycols.

4. Compositions as claimed in claim 1 or 2, in which the lipophilic matrix consists of compound selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, mono-, di- or triglycerids of fatty acids, the polyethoxylated derivatives thereof, waxes, cholesterol derivatives.

5. Compositions as claimed in any one of the above claims, in which the hydrophilic matrix consists of hydrogel-forming compounds.

6. Compositions as claimed in claim 5 in which the hydrophilic matrix consists of compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkylcellulose, carboxyalkylcellulose, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, natural or synthetic gums, polyalcohols.

7. Compositions as claimed in any one of the above claims, comprising a gastro-resistant coating.

8. Compositions as claimed in claim 7, in which the gastro-resistant coating consists of methacrylic acid polymers or cellulose derivatives.

9. Compositions as claimed in any one of the above claims, in which the active ingredient is wholly contained in the lipophilic amphiphilic matrix, in the form of tablets, capsules or minitablets.

10. Compositions as claimed in any one of claims 1 to 8 in which the active ingredient is dispersed both in the hydrophilic matrix and in the lipophilic/amphiphilic matrix, in the form of tablets, capsules or minitablets.

11. Compositions as claimed in any one of the above claims, in which the active ingredient belongs to the therapeutical classes of analgesics, antitussives, bronchodilators, antipsychotics, selective β 2 antagonists, calcium antagonists, antiparkinson drugs, non-steroidal antiinflammatory drugs, antihistamines, antidiarrheals and intestinal antiinflammatories, spasmolytics, anxiolytics, oral antidiabetics, cathartics, antiepileptics, topical antimicrobials.

12. Compositions as claimed in claim 10, in which the active ingredient is selected from mesalazine (5-aminosalicylic acid), budesonide, metformin, octylonium bromide, gabapentin, carbidopa, nimesulide, propionylcarnitine, isosorbide mono- and dinitrate, naproxen, ibuprofen, ketoprofen, diclofenac, chlorophenic acid, nimesulide, chlorhexidine, benzydamine, tibezonium iodide, cetylpyridinium chloride, benzalkonium chloride, sodium fluoride.

13. Compositions as claimed in any one of the above claims, containing bicadhesive substances.

14. Pharmaceutical compositions as claimed in the above claims, in the form of tablets chewable or erodible in the buccal cavity or in the first portion of the gastrointestinal tract.

Patentansprüche

1. Geschmacksmaskierte orale pharmazeutische Zusammensetzungen mit kontrollierter Freigabe, enthaltend einen aktiven Bestandteil, umfassend:

   a) eine Matrix, zusammengesetzt aus lipophilen Verbindungen mit einem Schmelzpunkt niedriger als 90°C, in der der aktive Bestandteil mindestens teilweise inglobatiert ist;

   b) eine amphiphile Matrix;

   c) eine hydrophile Außenmatrix, zusammengesetzt aus Hydrogelen, in der die lipophile Matrix und die amphiphile Matrix dispergiert sind;

   d) gegebenenfalls andere Exzipienten.

2. Geschmacksmaskierte Zubereitungen nach Anspruch 1, umfassend eine lipophile Matrix, eine amphiphile Matrix und eine hydrophile Matrix, wobei die lipophile Matrix aus C8-C20-Alkoholen oder C8-C20-Fettsäuren oder Estern von Fettsäuren mit Glycerin oder Sorbit oder anderen Polyalkoholen mit Kohlenstoffatomketten nicht höher als sechs zusammengesetzt ist.

3. Zusammensetzungen nach Anspruch 1 oder Anspruch 2, wobei die amphiphilen Verbindungen polare Lipide des Typs I oder II (Lecithin, Phosphatidylcholin, Phosphatidylethanolamin), Ceramide, Glykolalkyläther, Ester von Fettsäuren mit Polyäthylenglykolen oder Diäthylenglykolen sind.

4. Zusammensetzungen nach Anspruch 1 oder Anspruch 2, worin die lipophile Matrix aus einer Verbindung zusammengesetzt ist, ausgewählt aus ungesättigten oder hydrierten Alkoholen oder Fettsäuren, Salzen, Estern oder Amiden davon, Mono-, Di- oder Triglyceriden von Fettsäuren, polyethoxylierten Derivaten davon, Wachsen, Cholesterinderivaten.

5. Zusammensetzungen nach einem der obigen Ansprüche, wobei die hydrophile Matrix aus Hydrogelbildenden Verbindungen zusammengesetzt ist.

6. Zusammensetzungen nach Anspruch 5, wobei die hydrophile Matrix aus Verbindungen zusammengesetzt ist, ausgewählt aus Acryl- oder Methacrylsäurepolymeren oder -copolymeren, Alkylvinylpolymeren, Hydroxyalkylcellulose, Carboxyalkylcellulose, Polysacchariden, Dextrinen, Pectinen, Stärken und Derivaten, Alginsäure, natürlichem oder synthetischem Gummi, Polyalkoholen.

7. Zusammensetzungen nach einem der obigen An-

sprüche, umfassend einen gastroresistenten Überzug.

8. Zusammensetzungen nach Anspruch 7, wobei der gastroresistente Überzug aus Methacrylsäurepolymeren oder Cellulosederivaten zusammengesetzt ist.

9. Zusammensetzungen nach einem der obigen Ansprüche, wobei der aktive Bestandteil vollständig in der lipophilen amphiphilen Matrix enthalten ist, in Form von Tabletten, Kapseln oder Minitabletten.

10. Zusammensetzungen nach einem der Ansprüche 1 bis 9, wobei der aktive Bestandteil sowohl in der hydrophilen Matrix als auch in der lipophilen/amphiphilen Matrix dispergiert ist, in Form von Tabletten, Kapseln oder Minitabletten.

11. Zusammensetzungen nach einem der obigen Ansprüche, wobei der aktive Bestandteil zu der therapeutischen Klasse von Analgetika, Antitussiva, Bronchodilatatoren, Antipsychotika, selektiven β-2-Antagonisten, Calcium-Antagonisten, Anti-Parkinson-Arzneimitteln, nichtsteroiden antientzündlichen Arzneimitteln, Antihistaminen, Antidiarrhoika und intestinalen antientzündlichen Mitteln, Spasmolytika, Anxiolytika, oralen Antidiabetika, Abführmitteln, Antiepileptika, topischen antimikrobiellen Mitteln gehört.

12. Zusammensetzungen nach Anspruch 10, wobei der aktive Bestandteil ausgewählt wird aus Mesalazin (5-Aminosalicylsäure), Budesonid, Metformin, Octylonlumbromid, Gabapentin, Carbidopa, Nimesulid, Propionylcarnitin, Isosorbidmono- und -dinitrat, Naproxen, Ibuprofen, Ketoprofen, Diclofenac, Thiaprophensäure, Nimesulid, Chlorhexidin, Benzydamin, Tibezonlumiodid, Cetylpyridiniumchlorid, Benzalkoniumchlorid, Natriumfluorid.

13. Zusammensetzungen nach einem der obigen Ansprüche, enthaltend Bioklebesubstanzen.

14. Pharmazeutische Zusammensetzungen nach einem der obigen Ansprüche in Form von kaubaren Tabletten oder von Tabletten, die in der bukkalen Höhle oder im ersten Teil des gastrointestinalen Trakts erodierbar sind.

Revendications

1. Compositions pharmaceutiques administrables par voie orale à libération contrôlée et goût masqué contenant un ingrédient actif, comprenant :

   a) une matrice constituée de composés lipophiles avec un point de fusion inférieur à 90°C dans laquelle l'ingrédient actif est au moins partiellement englobé ;
   b) une matrice amphiphile ;
   c) une matrice hydrophile extérieure constituée d'hydrogels dans laquelle la matrice lipophile et la matrice amphiphile sont dispersées ;
   d) éventuellement d'autres excipients.

2. Formulations à goût masqué selon la revendication 1 comprenant une matrice lipophile, une matrice amphiphile et une matrice hydrophile, dans lesquelles la matrice lipophile est constituée de (C_8-C_{36}) alcools ou de (C_8-C_{36})acides gras ou esters d'acides gras avec du glycérol ou du sorbitol ou d'autres polyols avec une chaîne d'atomes de carbone non supérieure à six.

3. Compositions selon l'une quelconque des revendications 1 à 2 dans lesquelles les composés amphiphiles sont des lipides polaires de type I ou II (déolithine, phosphatidylcholine, phosphatidyléthanolamine), des céramides, des éthers alcyliques de glycol, des esters d'acides gras avec des polyéthylèneglycols ou des diéthylèneglycols.

4. Compositions selon la revendication 1 ou 2, dans lesquelles la matrice lipophile est constituée d'un composé choisi parmi les alcools insaturés ou hydrogénés ou les acides gras, sels, esters ou amides de ceux-ci, les mono-, di- ou tri-glycérides d'acides gras, les dérivés polyéthoxylés de ceux-ci, les cires, les dérivés du cholestérol.

5. Compositions selon l'une quelconque des revendications précédentes, dans lesquelles la matrice hydrophile est constituée de composés formant des hydrogels.

6. Compositions selon la revendication 5 dans lesquelles la matrice hydrophile est constituée de composés choisis parmi les polymères ou copolymères d'acide acrylique ou méthacrylique, les polymères alkylvinyliques, l'hydroxyalkylcellulose, la carboxyalkylcellulose, les polysaccharides, les dextrines, les pectines, les amidons et dérivés, l'acide alginique, les gommes naturelles ou synthétiques, les polyols.

7. Compositions selon l'une quelconque des revendications précédentes, comprenant un enrobage gastro-résistant.

8. Compositions selon la revendication 7, dans lesquelles l'enrobage gastro-résistant est constitué de polymères d'acide méthacrylique ou de dérivés de cellulose.

9. Compositions selon l'une quelconque des revendications précédentes, dans lesquelles l'ingrédient actif est entièrement contenu dans la matrice lipophilelamphiphile, sous forme de comprimés, de capsules ou de minicomprimés.

10. Compositions selon l'une quelconque des revendications 1 à 9 dans lesquelles l'ingrédient actif est dispersé à la fois dans la matrice hydrophile et dans la matrice lipophilelamphiphile, sous forme de comprimés, de capsules ou de minicomprimés.

11. Compositions selon l'une quelconque des revendications précédentes, dans lesquelles l'ingrédient actif appartient aux classes thérapeutiques des analgésiques, antitussifs, bronchodilatateurs, antipsychotiques, β_2-antagonistes sélectifs, antagonistes du calcium, antiparkinsoniens, antiinflammatoires non stéroïdiens, antihistaminiques, antidiarrhéiques et antiinflammatoires intestinaux, spasmolytiques, anxiolytiques, antidiabétiques oraux, cathartiques, antiépileptiques, antimicrobiens topiques.

12. Compositions selon la revendication 10, dans lesquelles l'ingrédient actif est choisi parmi la mésalazine (acide 5-aminosalicylique), le budésonide, la metformine, le bromure d'octylonium, la gabapentine, le carbidopa, le nimésulide, la propionylcarnitine, le mono- et dinitrate d'isosorbide, le naproxène, l'ibuprofène, le kétoprofène, le diclofénac, l'acide thiaprofénique, le nimésulide, la chlorhexidine, la benzydamine, l'flocure de tibézonium, le chlorure de cétylpyridinium, le chlorure de benzalkonium, le fluorure de sodium.

13. Compositions selon l'une quelconque des revendications précédentes, contenant des substances bioadhésives.

14. Compositions pharmaceutiques selon l'une quelconque des revendications précédentes, sous forme de comprimés croquables ou érodables dans la cavité buccale ou dans la première partie du tractus gastrointestinal.